

## **REMARKS**

### **Amendments**

Claim 1 is amended to delete the superfluous definition of R<sup>4</sup>. Claims 1 and 23 are also amended to recite pharmaceutically usable salts. Claim 26 is amended to correct an obvious typographical error. Claims 40-41 are amended to delete references to derivatives and solvates. Finally, claim 45 is amended to recite that R<sup>3</sup>, rather than R<sup>4</sup>, is H.

New method claims 61-69 recite individual methods of treatment listed in claim 31. New claim 70 is directed to further aspects of applicants' invention. See, for example, the exemplified compounds in the specification.

### **Rejection under 35 USC 112, first paragraph**

Claims 30, 31, 40, and 41 are rejected under 35 USC 112, first paragraph, as allegedly lacking enablement. This rejection is respectfully traversed.

The rejection appears to be incomplete. It is stated in the rejection that the claims allegedly contain subject matter which is "not described in the specification in such a way as to enable one skilled in the art ... to make and/use the invention." The rejection does not expressly state what subject matter is allegedly not enabled. However, the comments in the rejection refer to the treatment of cancer. Thus, applicants assume that the claims are rejected on grounds of lack of enablement with respect to the claimed methods of treating cancer. It is noted that new method claims 61-69 do not recite the treatment of tumors.

In the rejection, reference is made to the so-called Wands factors. These factors are used to determine whether undue experimentation is involved. See, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). However, before the issue of undue experimentation arises, the PTO must first present reasons to doubt the veracity of the objective enablement statements presented in an applicants' specification.

In making a lack of enablement rejection, it is the initial burden of the PTO to establish a reason to doubt the truth of the statements presented in the specification concerning enablement. It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure. As clearly and succinctly stated by the court in *In re*

*Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

As a matter of Patent Office practice, then a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented **must be taken in compliance with the enabling requirement of the first paragraph of §112, unless** there is reason to doubt the objective truth of statements contained therein relied on for enabling support. (emphasis in original)

See also, for example, *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995), and *Fiers v. Revel*, 984 F.2d 1164, 24 USPQ2d 1601 (Fed. Cir. 1993). Furthermore, as stated in *Marzocchi*, at 370, the PTO must have adequate support (evidence or reasoning) for its challenge to the credibility of applicants' statements of utility. See also *In re Bundy*, 209 USPQ 48 (CPA 1981). Additionally, working examples are not required to establish enablement. As stated by the court *Marzocchi*, at 369:

The first paragraph of §112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.

See also MPEP § 2164.02 which acknowledges that compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed.

Thus, all that is required under the statute is objective enablement. In addition, merely because an art is alleged to be unpredictable, this does not establish non-enablement. See, e.g., *In re Angstadt*, 190 USPQ 214, 219 (CCPA 1976) in which the art involved (catalysis) was acknowledged to be unpredictable, yet the court still found the disclosure in question to be enabling.

With respect to the amount of experimentation, applicants note that it is by now well settled law that the test for enablement is not whether any experimentation is needed, but whether the amount of experimentation required is undue. See *Angstadt*. Even a considerable amount of experimentation, or complex experimentation, is permissible if it is routine. See, e.g., *Ex parte Jackson*, 217 USPQ 804, 807 (POBA 1982) and *In re Wands*, 8 USPQ 2d 1400, 1404 (Fed. Cir. 1988).

In the rejection, it is argued that the state of the art for treating cancer is unpredictable. As mentioned above, an assertion that the relevant art is unpredictable does not by itself

establish lack of enablement under the statute.

The rejection also argues that there specification does not present working examples. As noted above, working examples are not required for enablement as indicated by the court in *Marzocchi* and by the PTO in MPEP § 2164.02.

It is further asserted in the rejection that the guidance in the specification with respect to enablement is limited to *in vitro* activity of the claims compounds as inhibitors of Factor Xa. Applicants disagree.

For example, the specification discloses there are compounds that are known in the art to possess antithrombotic and factor Xa inhibitory activity, including compounds of such structures as aromatic amidines, cyclic guanidines, and aromatic heterocycles. See page 4, lines 1-15. Further, applicants' specification further states that Factor Xa is known to be one of the proteases involved in blood coagulation and that Factor Xa catalyses the conversion of prothrombin into thrombin, which in turn is involved in thrombus formation. Inhibition of Factor Xa can thus prevent formation of thrombin.

Applicants' specification further discloses that there are methods known for measuring thrombin inhibition (for example by the method of G. F. Cousins et al. in *Circulation* **1996**, 94, 1705-1712) as well as known conventional *in-vitro* or *in-vivo* methods for measuring the inhibition of factor Xa and measuring anticoagulant and antithrombotic activity (for example, by J. Hauptmann et al. in *Thrombosis and Haemostasis* **1990**, 63, 220-223; T. Hara et al. in *Thromb. Haemostas.* **1994**, 71, 314-319). See pages 4-5 of the specification.

In addition, applicants' specification discloses that the compounds according to the invention may be used for the treatment of tumours, tumour diseases and/or tumour metastases, and cites several references that describe an antitumoural action of TF-VII and Factor Xa inhibitors of various types of tumour. See page 6 of the specification.

Thus, the specification clearly demonstrates that the art recognizes a correlation between the activity of the compounds and the treatment of certain diseases. Although the rejection implies a lack of guidance, it is evident that the specification provides guidance to enable one of ordinary skill in the art to measure and determine the level of activity of the claimed compounds. The rejection does not demonstrate why such guidance would not be sufficient for objective enablement as required under the statute. Moreover, the rejection

does not provide a reason to doubt the veracity of the enablement statements in the specification.

Enablement is viewed in the context of what one of ordinary skill in the art knows. Such persons of ordinary skill in the art can, for example, make the compounds of the claimed genus and determine their activity levels for use in the claimed methods based on, for example, the disclosure contained in applicants' own specification, publications cited therein and knowledge within the art,. See, for example, *Spectra-Physics v Coherent*, 827 F.2d 1524, 3 USPQ2d 1737 (Fed. Cir. 1987). See also *Amgen v Hoechst Marion Roussel*, 65 USPQ2d 1385 (CA FC 2003) holding that the:

...specification need not explicitly teach those in the art to make and use the invention; the requirement is satisfied if, given what they already know, the specification teaches those in the art enough that they can make and use the invention without 'undue experimentation.

In view of the above remarks, it is respectfully submitted that applicants' disclosure provides more than sufficient guidance to objectively enable one of ordinary skill in the art to make and use the claimed invention with no more than routine experimentation. Withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

#### **Rejection under 35 USC 112, first paragraph**

Claims 40 and 41 are rejected under 35 USC 112, first paragraph, as allegedly lacking enablement with respect to solvates. This rejection is respectfully traversed for the reasons of record.

However, for purposes of furthering prosecution, claims 40 and 41 are amended to delete references to solvates. These amendments render the instant rejection moot. Withdrawal of the rejection is requested.

#### **Obviousness-type Double Patenting Rejection in view of US 7,504,500**

Claim 26 is rejected as being obvious in view of claims 1-17 and 21-23 of US 7,504,500 (Mederski et al.). This rejection is respectfully traversed.

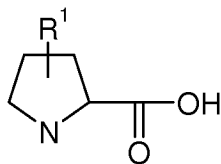
Firstly, it is noted that US 7,504,500 has only 20 claims. Applicants assume that the reference to claims 21-23 of US 7,504,500 is a typographical error.

In the rejection, it is argued that US 7,504,500 discloses a process for making a

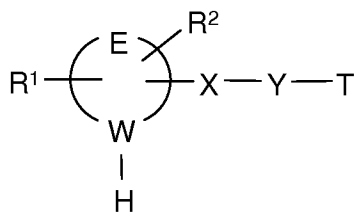
“group of compounds which include species within the instant claims.” Applicants understand this argument to be asserting that the process claimed by US ‘500 is directed towards making a group of compounds that includes compound(s) that fall within the group of compounds that are made by applicants’ claim 26. This argument does not, however, demonstrate that the process steps recited in claims 1-17 of US ‘500 suggest or render obvious the process steps recited in applicants’ claim 26. A mere assertion that there is one known process for making a compound does not establish that all other processes for making that compound are *per se* obvious.

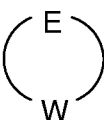
The rejection further asserts that the claims of US ‘500 “are drawn to a genus, of which embodiments fall within the scope of the instant claims.” Applicants understand this argument to be asserting that the process claimed by US ‘500 encompasses process embodiments that fall within the scope of applicants’ claim 26. Applicants disagree.

For example, independent claims 1 and 16 of US ‘500 recites a two step process wherein a compound of a Formula II is reacted with a compound of Formula III to obtain a compound of Formula IV, and then the compound of Formula IV is reacted with a compound of Formula V to obtain the desired compound, i.e., a compound of Formula I or Ia. In this reaction process, the compound of Formula II is of the following formula:



Conversely, applicants’ claim 26 recites a one step process wherein a compound of a Formula II is reacted with a compound of a Formula III to obtain the desired compound, i.e., a compound of Formula I. In this reaction process, the compound of Formula II is of the following formula:



It is noted that in this formula, the group  can be pyrrolidine-1,2-diyl. However, the

group X is CONH; Y is 1,3- or 1,4-phenylene which is unsubstituted or monosubstituted or disubstituted by methyl, trifluoromethyl, ethyl, propyl, Cl or F; and T is morpholin-4-yl which is monosubstituted or disubstituted by carbonyl oxygen. Compounds of such structures are not within the genus of Formula II of US '500.

Thus, applicants' one step process is clearly distinguishable from the two step process embodiments of claims 1-17 of US '500. Additionally, compounds of applicants' Formula II are not employed in the process of claims 1-17 of US '500. Hence, the process claimed by US '500 **does not encompass or suggest** process embodiments that fall within the scope of applicants' claim 26.

Finally, the rejection asserts that the embodiments claimed by US '500 suggests applicants' claimed invention, and, therefore, the applicants' claim 26 is *prima facie* obvious in view of claims of US '500. These are unsupported conclusory statements. The arguments presented in the rejection do not establish that the claims of US '500 render obvious the process of applicants' claim 26.

In view of the above remarks, it is respectfully submitted that none of the claims of US '500 render obvious applicants' claim 26. Withdrawal of the rejection is respectfully requested.

#### **Obviousness-type Double Patenting Rejection in view of SN 11/576,207**

Claims 1, 23, 26, 29-33 and 40-60 are provisionally rejected as being obvious in view of claims 1-9 and 11-36 of Serial No. 11/576,207, March 28, 2007. This rejection is respectfully traversed.

This rejection is a provisional rejection in view of a later filed application. See MPEP 804(I)(B)(1) wherein it is stated that:

“If a ‘provisional’ nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer.”

Thus, withdrawal of the rejection is respectfully requested.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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